

EXHIBIT E

**United States Patent [19]**

Chee et al.

[11] Patent Number: **5,795,716**
 [45] Date of Patent: **Aug. 18, 1998**

[54] COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

WO 92/10588 6/1992 WIPO
 95/11995 5/1995 WIPO
 WO 95/35505 12/1995 WIPO

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[21] Appl. No.: **327,525**

[22] Filed: **Oct. 21, 1994**

[51] Int. Cl.⁶ C12Q 1/68; C12P 19/34;
 G06F 15/46; C07H 21/04

[52] U.S. Cl. 435/6; 435/91.1; 435/91.2;
 382/178; 382/179; 364/96; 364/97; 364/98;
 364/99; 536/24.3; 536/24.33; 536/24.32;
 536/23.1

[58] Field of Search 382/178, 179;
 435/5, 6, 91.2, 91.1, 7.1, 7.2, 23.1; 536/24.3,
 24.33, 96, 97, 98, 99

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Primary Examiner—W. Gary Jones
Assistant Examiner—Dianne Rees

[57] **ABSTRACT**

A computer system for analyzing nucleic acid sequences is provided. The computer system is used to perform multiple methods for determining unknown bases by analyzing the fluorescence intensities of hybridized nucleic acid probes. The results of individual experiments are improved by processing nucleic acid sequences together. Comparative analysis of multiple experiments is also provided by displaying reference sequences in one area and sample sequences in another area on a display device.

10 Claims, 26 Drawing Sheets

**Microfiche Appendix Included
 (5 Microfiche, 272 Pages)**

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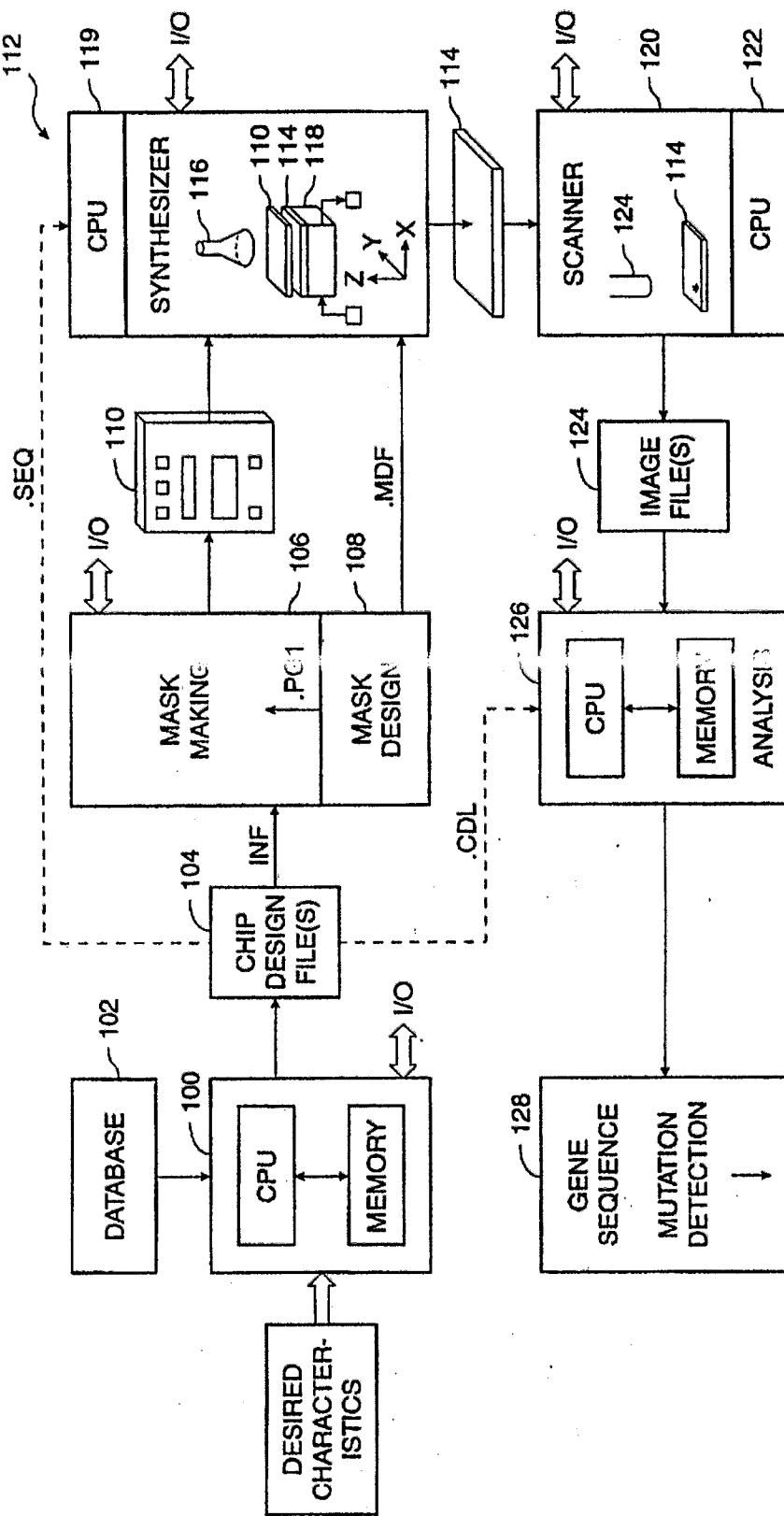


FIG. 1

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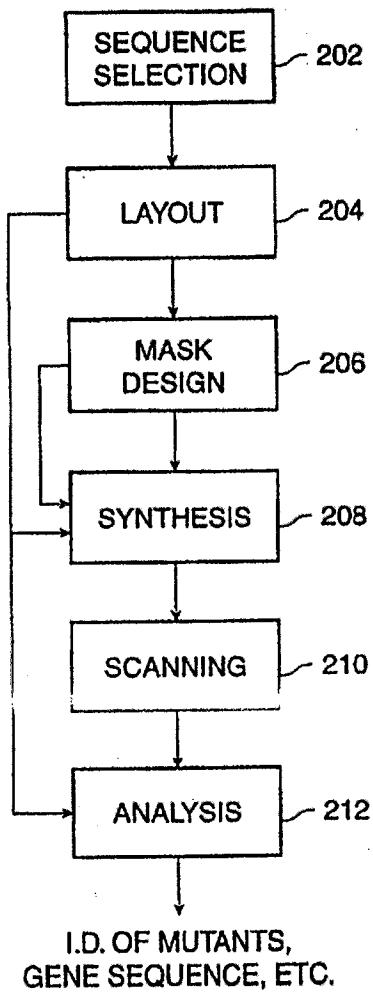


FIG. 2A

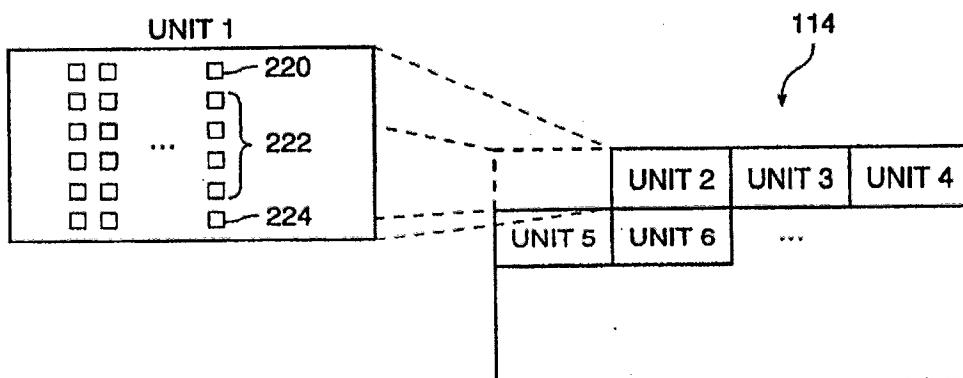


FIG. 2B

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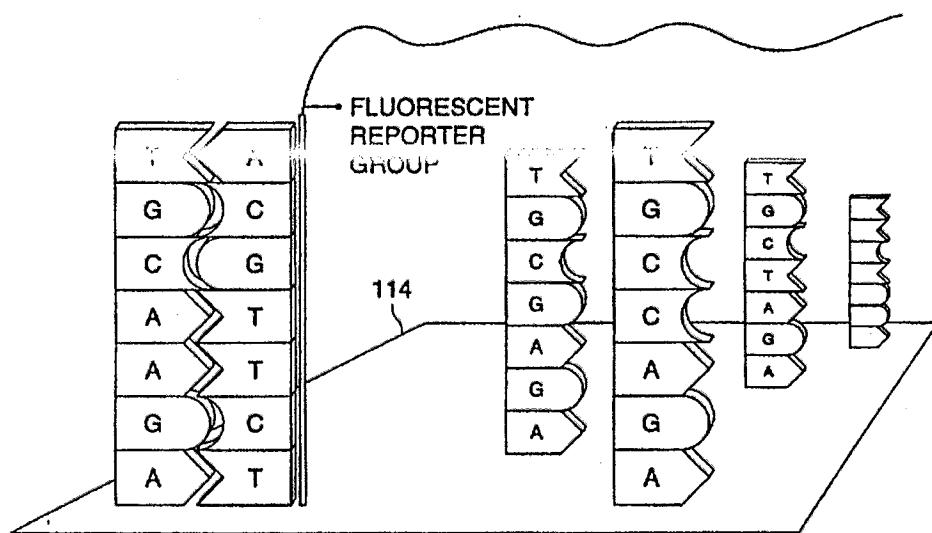


FIG. 2C

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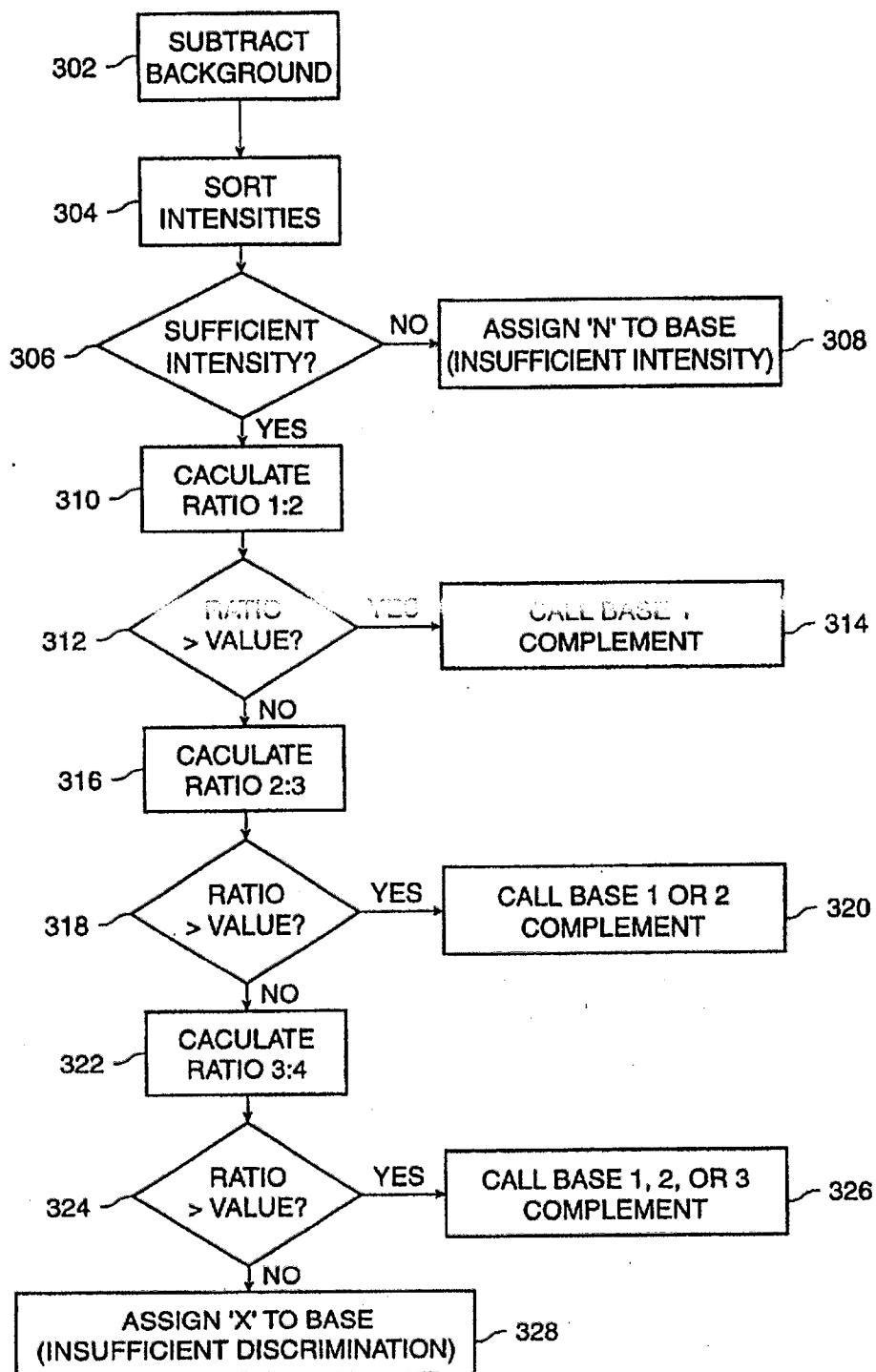


FIG. 3

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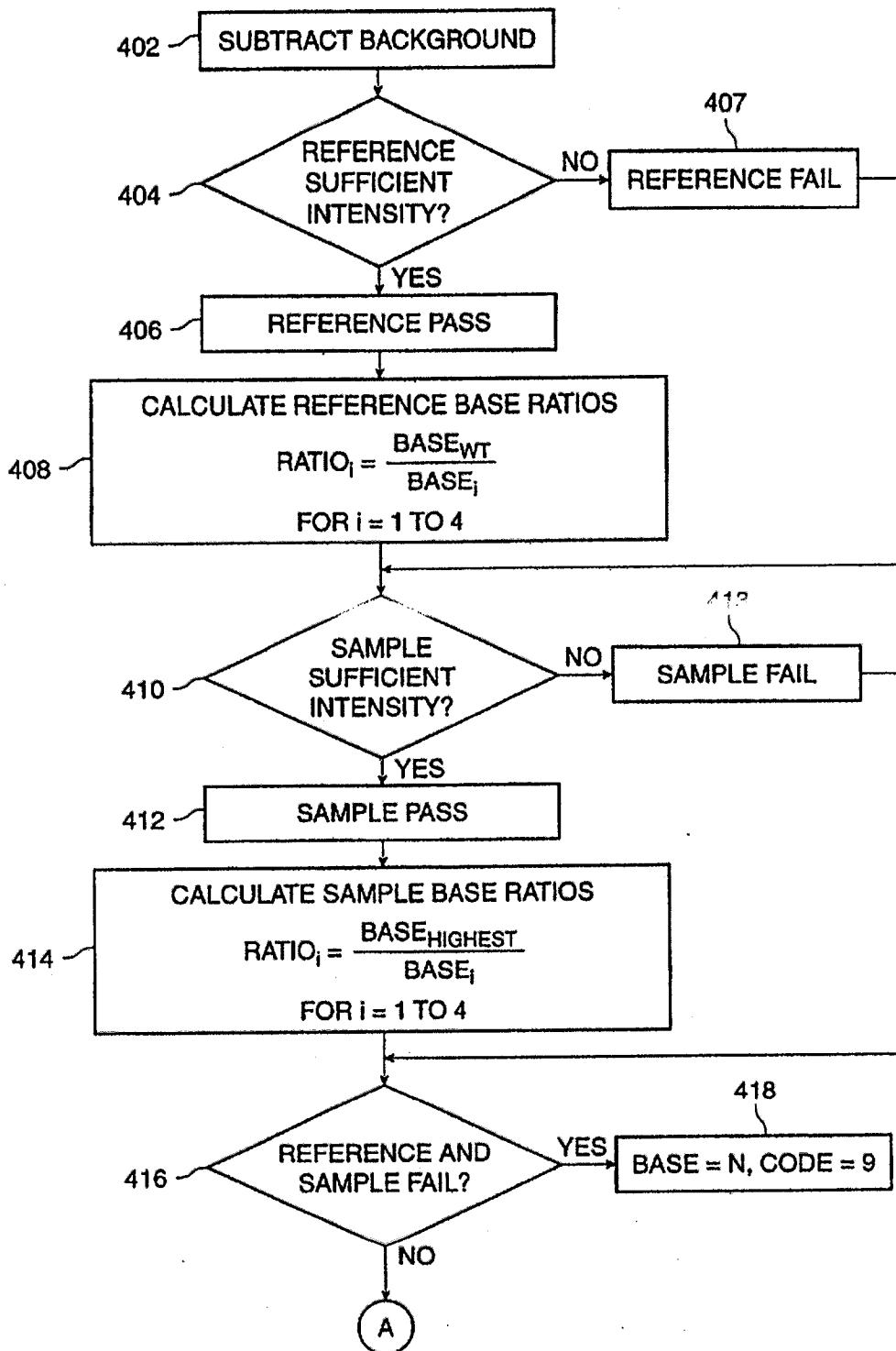


FIG. 4A-1

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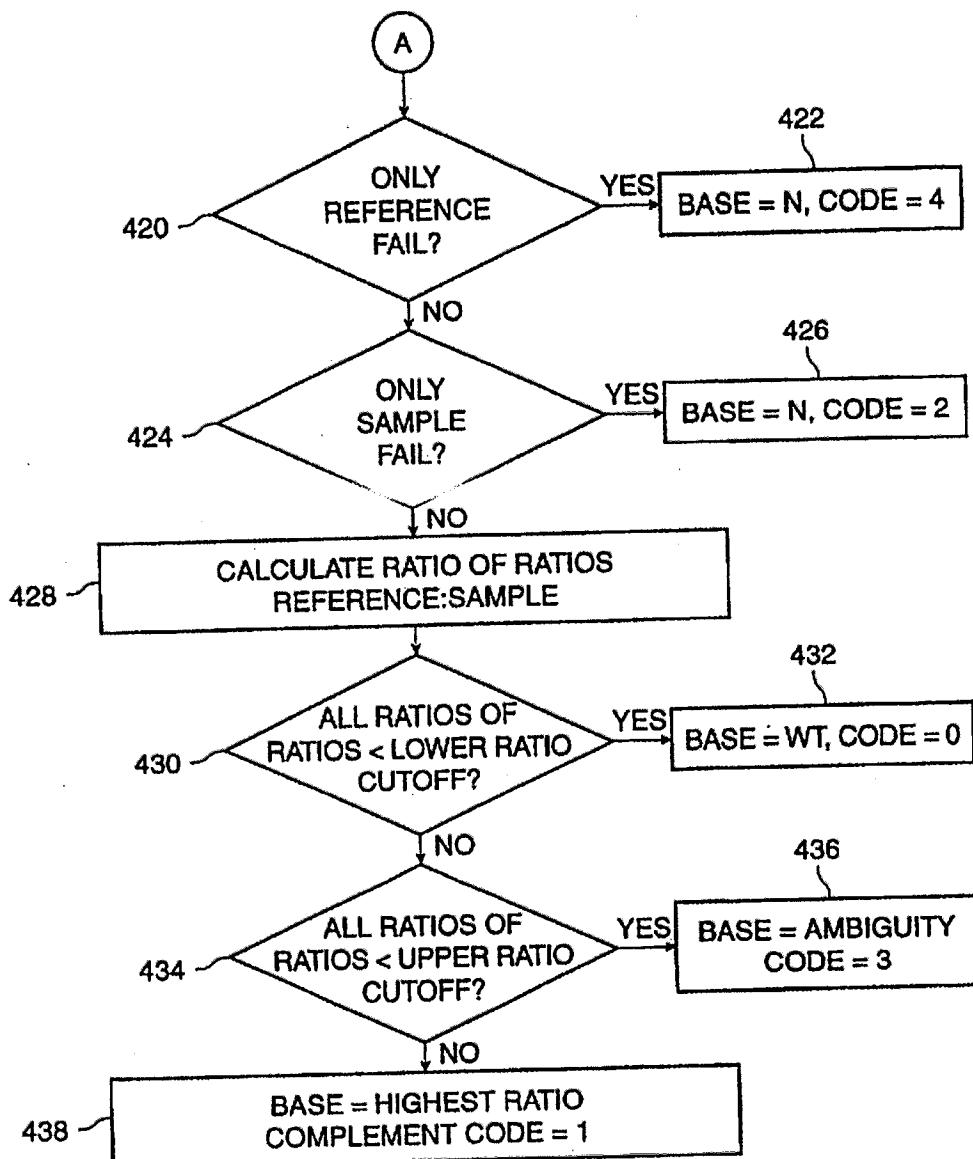


FIG. 4A - 2

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POSITION	WT	REFERENCE				SAMPLE				RATIO OF RATIOS							
		BACK-GROUND	A	C	G	T	BACK-GROUND	A	C	G	T	A/A	C/C	G/G	T/T	BASE	CONFIDENCE
463	C	P	7.2	9.9	1.0	5.6	P	6.4	2.3	1.0	14.5	1.1	4.3	1.0	0.4	G	1
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18

F/G. 4B

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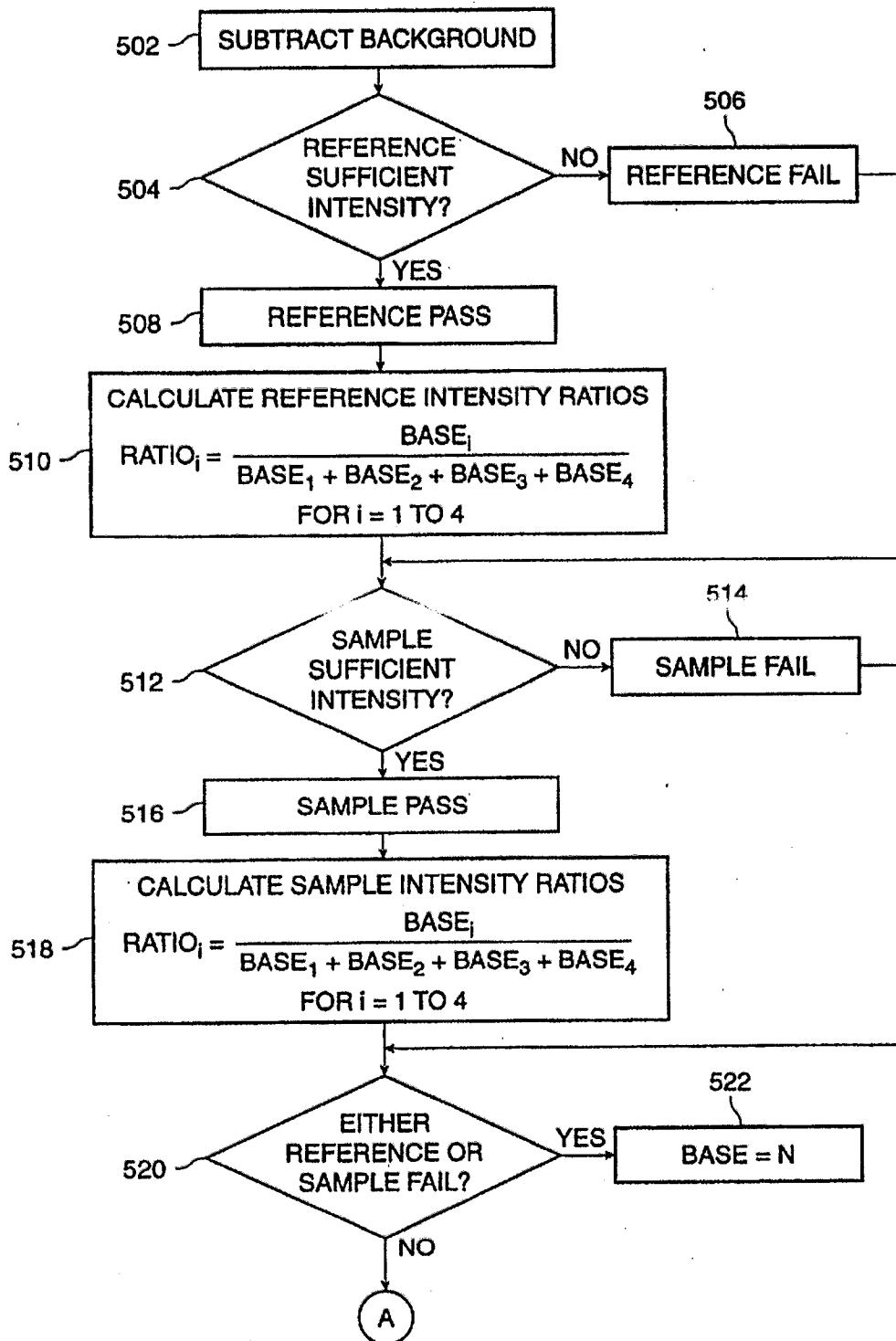
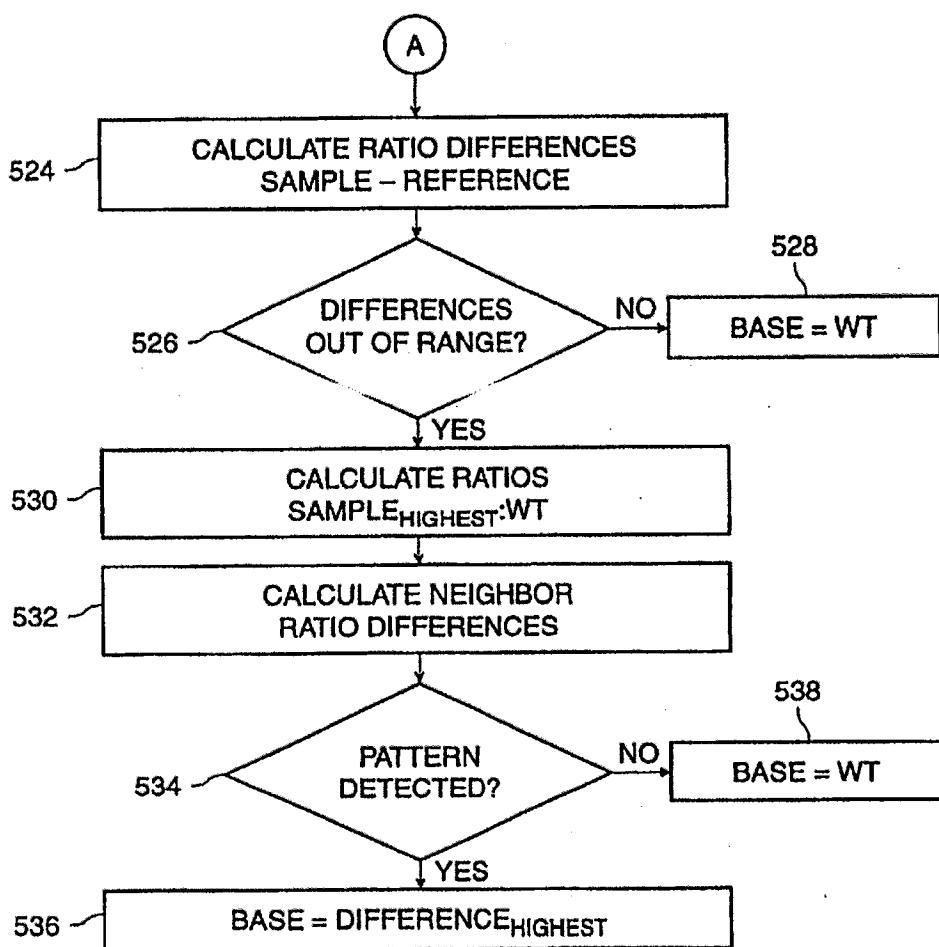


FIG. 5A - I

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5,795,716**FIG. 5A - 2**

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NORMALIZED INTENSITIES																			
WILDTYPE																			
A		0.61	0.57	0.70	0.08	0.13	0.11	0.75	0.57	0.5	0.10	0.07	0.87	0.06	0.75	0.20	0.26	0.37	
C		0.24	0.29	0.18	0.81	0.66	0.80	0.10	0.15	0.3	0.83	0.90	0.07	0.88	0.09	0.29	0.51	0.42	
G		0.11	0.09	0.08	0.08	0.12	0.05	0.07	0.16	0.7	0.04	0.03	0.06	0.04	0.10	0.16	0.12	0.13	
T		0.04	0.04	0.04	0.03	0.08	0.04	0.07	0.12	0.4	0.02	0.01	0.01	0.03	0.05	0.36	0.11	0.09	
MUTANT																			
A		0.37	0.37	0.55	0.15	0.26	0.26	0.58	0.25	0.6	0.16	0.16	0.83	0.05	0.64	0.21	0.26	0.37	
C		0.40	0.45	0.27	0.71	0.46	0.57	0.15	0.15	0.19	0.72	0.80	0.09	0.80	0.12	0.28	0.46	0.34	
G		0.18	0.11	0.12	0.10	0.15	0.11	0.13	0.44	0.5	0.08	0.05	0.06	0.10	0.10	0.13	0.19	0.15	0.16
T		0.05	0.06	0.06	0.04	0.13	0.06	0.14	0.16	0.9	0.03	0.02	0.02	0.05	0.11	0.32	0.14	0.12	
MT - MT (NORMALIZED INTENSITIES)																			
POSITION:		234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	
WILDTYPE:		A	A	C	C	C	C	A	A	T	C	C	A	C	A	T	C	A	
CALLED:		M	M	A	C	X	C	A	X	C	C	C	A	C	A	X	X	M	
A		0.24	-0.20	-0.15	0.07	0.12	0.15	-0.18	-0.32	0.9	0.06	0.07	-0.04	0.00	-0.11	0.01	0.00	0.01	
C		0.17	0.16	0.09	-0.10	-0.20	-0.23	0.05	0.00	-0.4	-0.11	-0.10	0.03	-0.08	0.03	-0.01	-0.05	0.07	
G		0.07	0.02	0.04	0.02	0.03	0.03	0.03	0.28	0.9	0.04	0.01	0.00	0.06	0.03	0.03	0.03	0.03	
T		0.01	0.02	0.02	0.01	0.05	0.02	0.07	0.04	-0.14	0.01	0.01	0.02	0.05	-0.04	0.03	0.04		

FIG. 5B

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BCK SUBTRACTED INTENSITIES																			
POSITION:	RY090203.CQ1	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	
WILDTYPE:	A	A	A	C	C	C	A	A	A	T	C	C	A	C	A	T	C	A	
CALLED:	A	A	A	C	C	C	A	A	A	T	C	C	A	C	A	T	C	M	
A	148	193	165	17	70	38	282	385	97	31	18	158	15	223	178	126	154		
C	57	100	42	167	345	278	38	99	135	249	249	13	244	28	257	250	175		
G	26	32	20	16	64	17	27	107	100	13	9	11	10	30	142	59	55		
T	9	15	10	6	41	14	27	79	261	6	2	1	7	16	320	52	37		
S	240	340	238	207	522	347	374	671	598	298	279	182	276	298	896	487	421		
WTR	148	193	165	167	345	278	282	385	261	249	249	158	244	223	320	250	154		
MAXR	148	193	165	167	345	278	282	385	261	249	249	158	244	223	320	250	175		
MC090407.CQ1																			
POSITION:	RY090203.CQ1	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	
WILDTYPE:	A	A	A	C	C	C	A	A	A	T	C	C	A	C	A	T	C	A	
CALLED:	M	M	A	C	X	C	A	X	X	Y	C	C	C	A	C	A	X	M	
A	194	238	150	44	191	126	283	332	234	58	49	242	25	337	286	180	256		
C	209	291	74	202	337	277	74	199	171	259	288	27	376	65	379	324	234		
G	92	72	34	29	114	52	65	571	23	30	17	16	47	71	254	104	109		
T	25	39	16	11	96	29	68	205	267	11	8	5	23	57	427	97	85		
S	520	639	274	286	738	484	489	1307	907	357	362	291	472	529	1346	705	684		
WTE	194	238	150	202	337	277	283	332	267	259	288	242	376	337	427	324	256		
MAXE	194	238	150	202	337	277	283	332	267	259	288	242	376	337	427	324	256		

FIG. 5B-1

502A

502B

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WTENWTR	1.31	1.23	0.91	1.21	0.98	1.00	1.00	0.86	1.02	1.04	1.15	1.54	1.51	1.34	1.30	1.66	
MAXENWTR	1.42	1.51	0.91	1.21	0.98	1.00	1.00	1.48	1.02	1.04	1.15	1.54	1.51	1.34	1.30	1.66	
N-L + N-R	0.79	-0.63	0.54	-0.25	0.01	0.14	0.94	0.11	0.10	0.27	0.38	0.04	0.14	-0.13	-0.40	530	
N-L	0.09	-0.60	0.30	-0.24	0.02	0.01	0.48	-0.45	0.02	0.11	0.38	0.01	0.04	-0.17	-0.04	532	
N-R	0.60	-0.30	0.24	-0.02	-0.01	0.48	0.46	-0.12	-0.11	-0.38	-0.01	0.04	0.17	0.04	-0.36		
N-L D(N-R)	-0.90	0.54	-0.25	0.01	0.48	0.94	-0.43	-0.10	-0.27	0.38	0.04	0.14	-0.13				
N-R D(N-L)	-0.90	0.54	-0.25	0.01	0.48	0.94	-0.43	-0.10	-0.27	0.38	0.04	0.14	-0.13				
L(N-L) - (N-R)L	0.29	0.07	0.22	0.02	0.49	0.02	0.44	0.13	0.50	0.39	0.03	0.21	0.21				
A+B-C	-2.10	1.01	-0.73	0.00	1.44	1.86	-1.0	-0.33	-1.03	0.36	0.06	0.06	-0.48				
SUM MT/ SUM WT INTENSITIES	2.16	1.88	1.15	1.39	1.41	1.39	1.31	1.95	1.52	1.20	1.30	1.60	1.71	1.78	1.50	1.45	1.63
NL + NR	2.50	1.45	2.18	2.04	2.05	1.61	2.77	2.04	1.71	1.89	2.18	2.03	2.22	1.88	1.85		
N-L + N-R	0.22	-0.48	0.10	0.02	0.03	-0.36	0.54	-0.03	-0.21	-0.10	0.10	0.02	0.17	0.11	-0.12		
N-L	-0.28	-0.73	0.21	0.03	-0.02	0.09	0.54	-0.43	-0.32	0.10	0.30	0.10	0.07	-0.27	-0.06		
N-R	0.73	-0.23	-0.03	0.02	0.09	-0.64	0.43	-0.52	-0.10	-0.30	-0.10	-0.07	0.27	0.06	-0.18		

FIG. 5B-2

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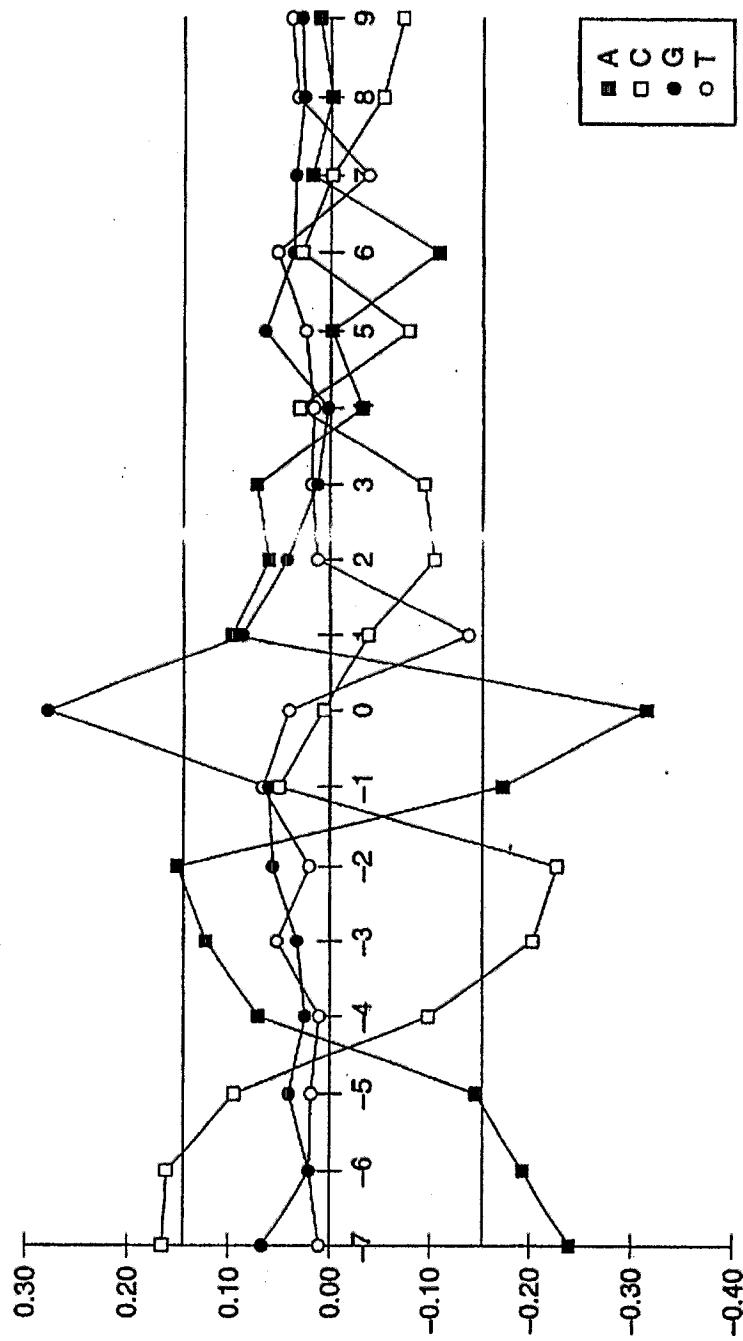


FIG. 5C

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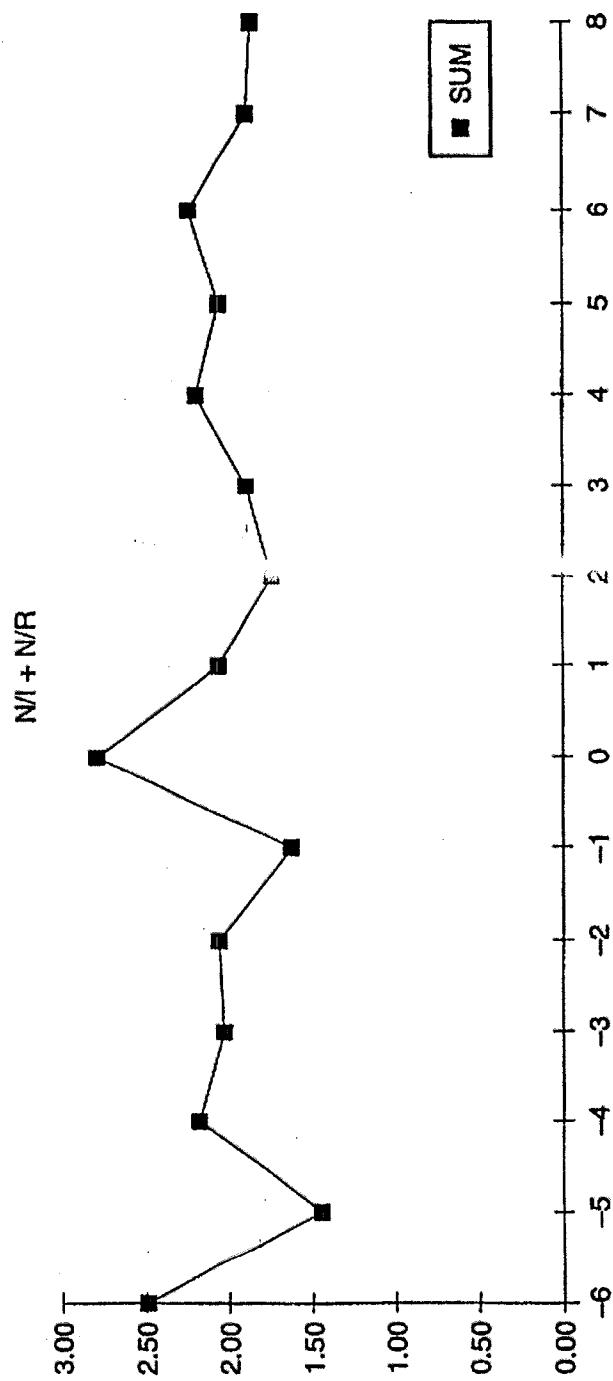


FIG. 5D

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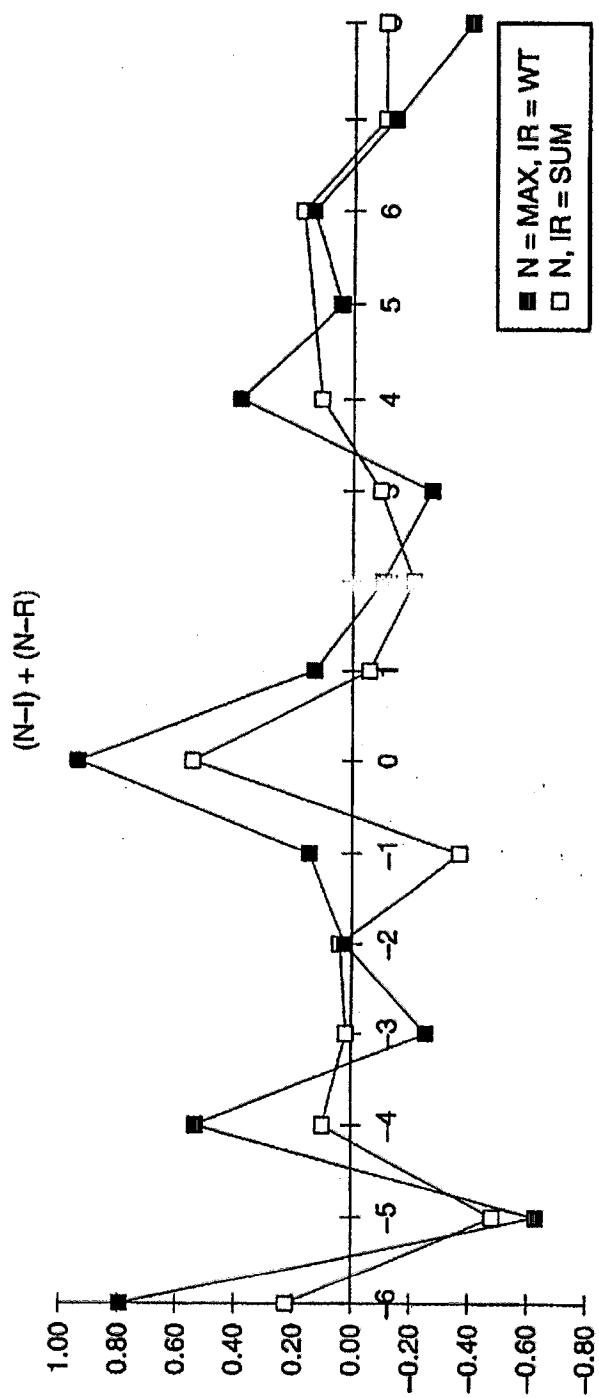


FIG. 5D-1